Product Development Plan for a mRNA Dengue Vaccine

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Incepta Pharmaceuticals Ltd

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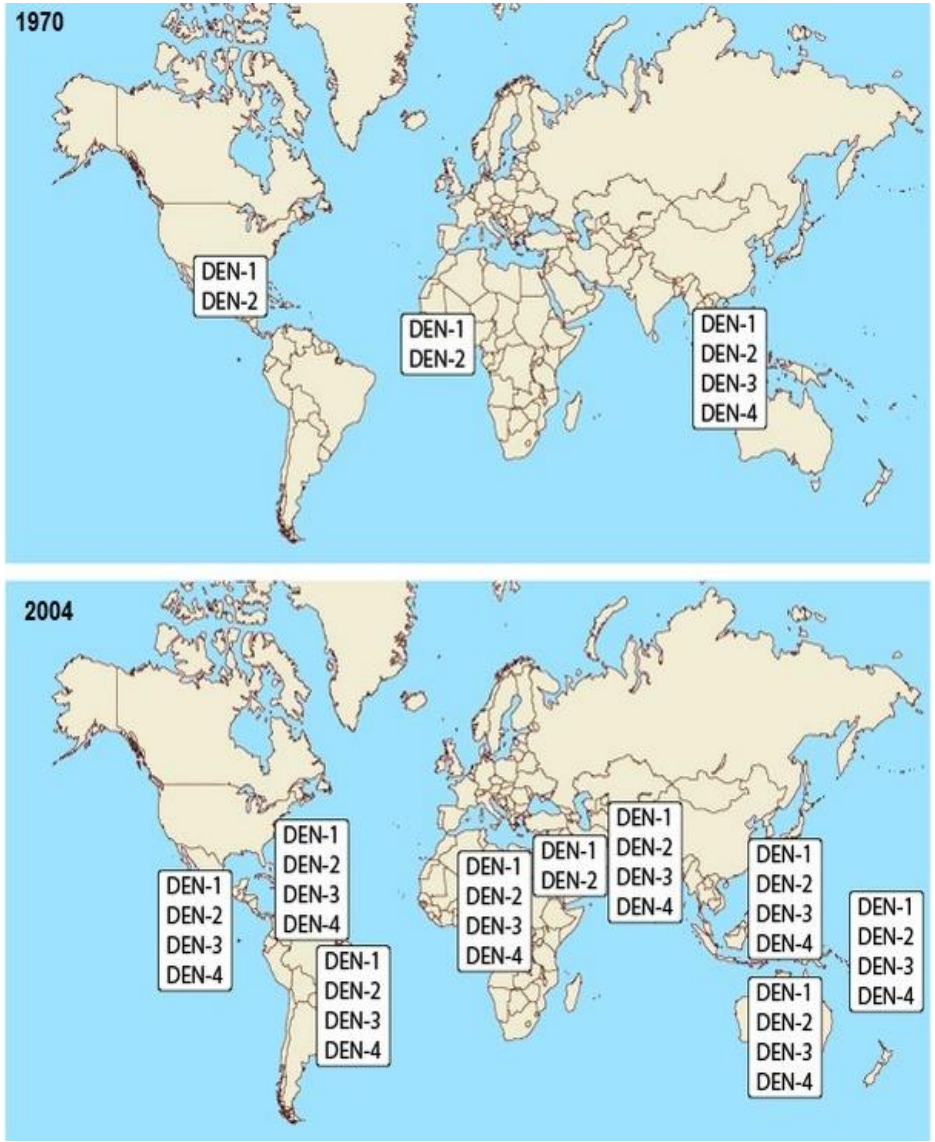
Global Dengue Burden

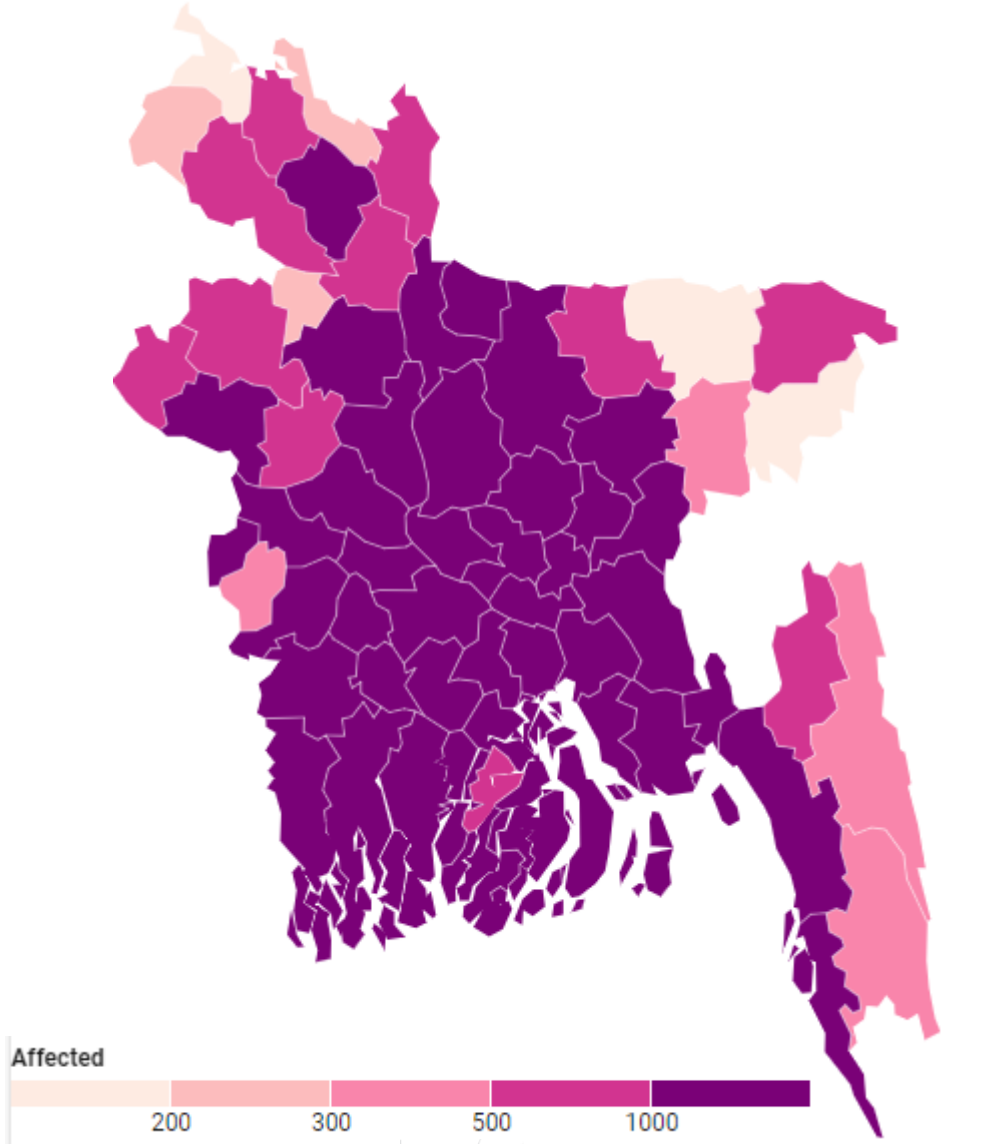
- First isolated in **1943**, increasing concern with rapid urbanization
- At present, endemic in more than **100 countries**
- **100-400 million** infections/year with **96 million** clinical manifestation
- Almost **half of world's population** at risk
- Asia represents **70%** of global disease burden



Source: WHO, PMID: 21079655

Dengue in Bangladesh

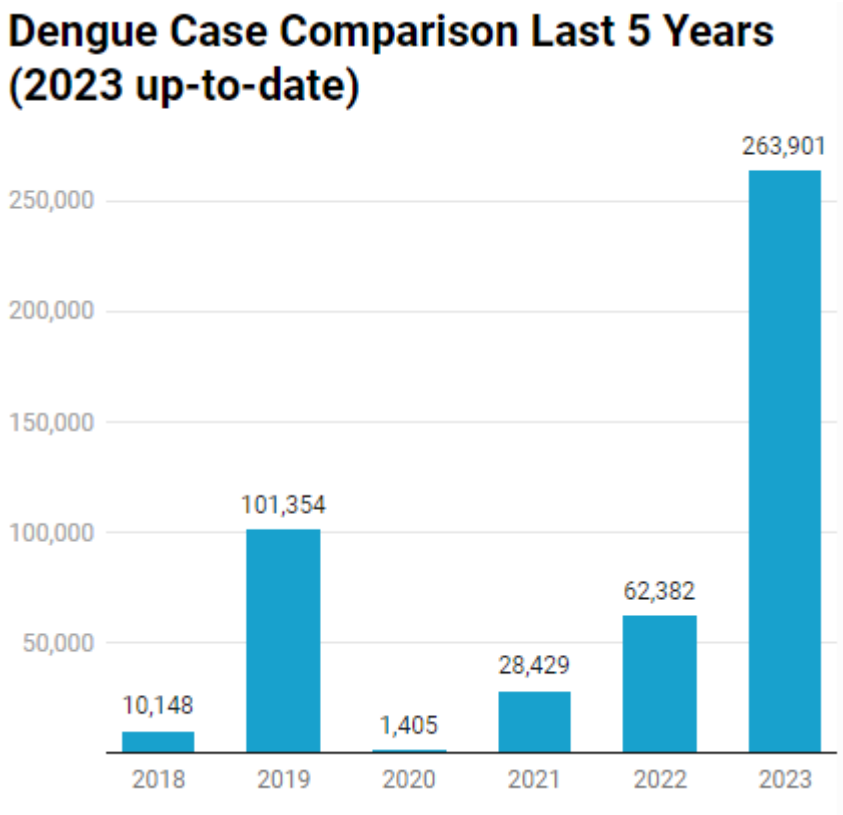
- Geographical location, weather, population density contributing together high number of cases
- First outbreak reported in **2000**, resulted **5551 cases** including **93 deaths**
- Mostly limited to capital Dhaka and very few metropolitan cities
- **In 2023, distributed all over the country**



Source: Directorate General of Health Services, Bangladesh

Current Dengue status in Bangladesh

- Dengue is costing **tremendous disease burden** each year
- In last 24 hours, **263901** hospitalization and **11** deaths
- Three main reason of high disease burden
  - ✓ No available **vaccine**
  - ✓ No available **therapeutics** for seriously ill hospitalized patients
  - ✓ No effective **vector control** strategy



Source: Directorate General of Health Services, Bangladesh

Bangladesh: Dengue Hotspot and Global Warning!

- In 2023, **Bangladesh** (170 million population) has **2.6 times higher cases** than neighboring country **India** (1.4 billion population)
- Among South-East Asia, Bangladesh is experiencing **maximum** dengue cases and deaths this year
- In the week of 36, US reported maximum number of dengue cases **(78)**, while Bangladesh reported **2575**
- Without vaccine research and trials, this situation can bring catastrophic disaster globally

Region/Country	Cases	Deaths
USA	1,289.00	-
Europe (Italy, France & Spain)	74.00	-
India	94,198.00	91.00
Bangladesh	247,032.00	1,206.00

Source: CDC; ECDC; DGHS, Bangladesh; NCVBDC, India

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Dengue Vaccine Development

- For more than 75 years, scientists and product developers have attempted to design and advance safe and efficacious vaccine candidates.
- Challenges have been substantial and formidable
  - ✓ Existence of four DENV types (1–4), each capable of causing infection
  - ✓ No validated immune correlate of protection
  - ✓ Animal models do not comprehensively recapitulate the human dengue infection experience
  - ✓ Immunologic assays are unable to precisely define DENV type-specific immune responses
  - ✓ Requirement for very large efficacy trials to demonstrate benefit across diverse populations and clinical endpoints

PMID: 37061527

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Dengue Vaccine Development

Name[a]	Year[b]	Valence[c]	Vaccine formulation	Developer/manufacturer	Evaluation	Adjuvanted
Dengvaxia	2015	Tetravalent	Chimeric viruses YFV/DEN 1–4	Sanofi Pasteur	Licensed	No
TV003/TV005	2003	Tetravalent	Three genetically attenuated viruses and one chimeric virus	NIAID[d] and Butantan[e]	*In vivo* (phase IIIB)	No
TAK-003	2006	Tetravalent	Chimeric viruses DEN-2 PDK-53, DEN -1,–3, or –4	Takeda	*In vivo* (phase II) To be licensed in Indonesia in 2023	No
TDEN	2017	Tetravalent	Viruses attenuated with passages in PDK cells	WRAIR[f] and GlaxosmithKline	*In vivo* (phase I-II)	No
DPIV	2012	Tetravalent	Purified inactivated viruses (DEN 1–4), Aluminium hydroxide AS01, AS03 or AS04 adjuvants	WRAIR, GllaxosmithKline and FIOcruz[g]	*In vivo* (phase I)	Yes
TVDV	2018	Tetravalent	DNA vaccine based on prM and E protein coding sequences cloned in VR1012 plasmid and co-administered with VAXFECTIN as an adjuvant	U.S. AMRDC[h], WRAIR, NMRC and Vical	*In vivo* (animal and phase I)	Yes
V180	2018	Tetravalent	Recombinant proteins based on prM and 80% of E protein of DEN 1–4 combined with different adjuvants	Merck and Co.	*In vivo* (phase I)	Yes
DSV4	2018	Tetravalent	Virus like particles expressing EDIII of DEN 1–4	International Centre for Genetic Engineering and Biotechnology	*In vivo* (animal)	No
E80-mRNA	2020	Tetravalent	mRNA expressing human IgE and E80 protein packaged into LNP	CAS laboratory of Molecular Virology and Immunology, Institute Pasteur of Shanghai	*In vivo* (animal)	No

- **Platforms**
  - ✓ Live attenuated
  - ✓ Inactivated
  - ✓ Protein subunit
  - ✓ DNA
  - ✓ mRNA

Only **live attenuated virus vaccines** have achieved licensure or reached advanced clinical development

PMID: 36857199

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Dengue Vaccine Development

- **Denvaxia**
  - ✓ First licensed vaccine; 20 countries
  - ✓ **Poor protection** in children under age of 9 years
  - ✓ Lower protection against **DENV1 & 2**; predominant Ab response against **DENV4**
- **TAK-003**
  - ✓ Licensed in Indonesia this year to be used in people 4 years of age and older regardless of **baseline dengue immune status**
  - ✓ No protection in seronegative recipients against all dengue and hospitalized dengue due to **DENV3**
  - ✓ No conclusive data for **DENV4** due to low event numbers during trial
- **LATV TV003/TV005**
  - ✓ Initiated Phase 3 study in 2016 with 16,000 volunteers in Brazil
  - ✓ Efficacy data is only available for **DENV1 (89.5%)** and **DENV2 (69.6%)** due to the low circulation of types **DENV3** and **4** during the trial

A more effective vaccine that can generate heterotypic nAb against all four DENV serotypes is still needed

PMID: 37061527, 36857199 and 34168334

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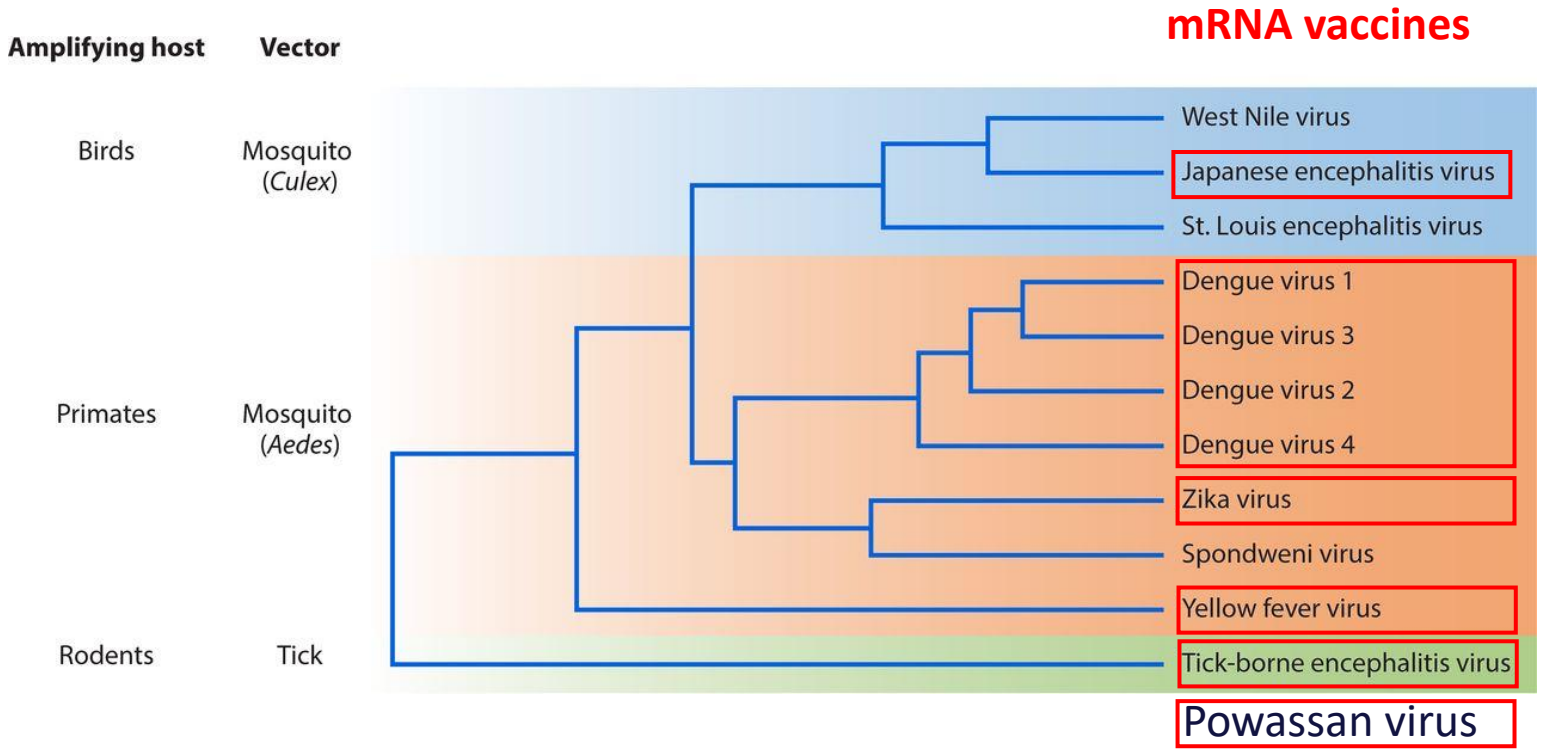
Dengue Vaccine Development

- Recent advances have updated **the mRNA vaccine development of many flaviviruses**



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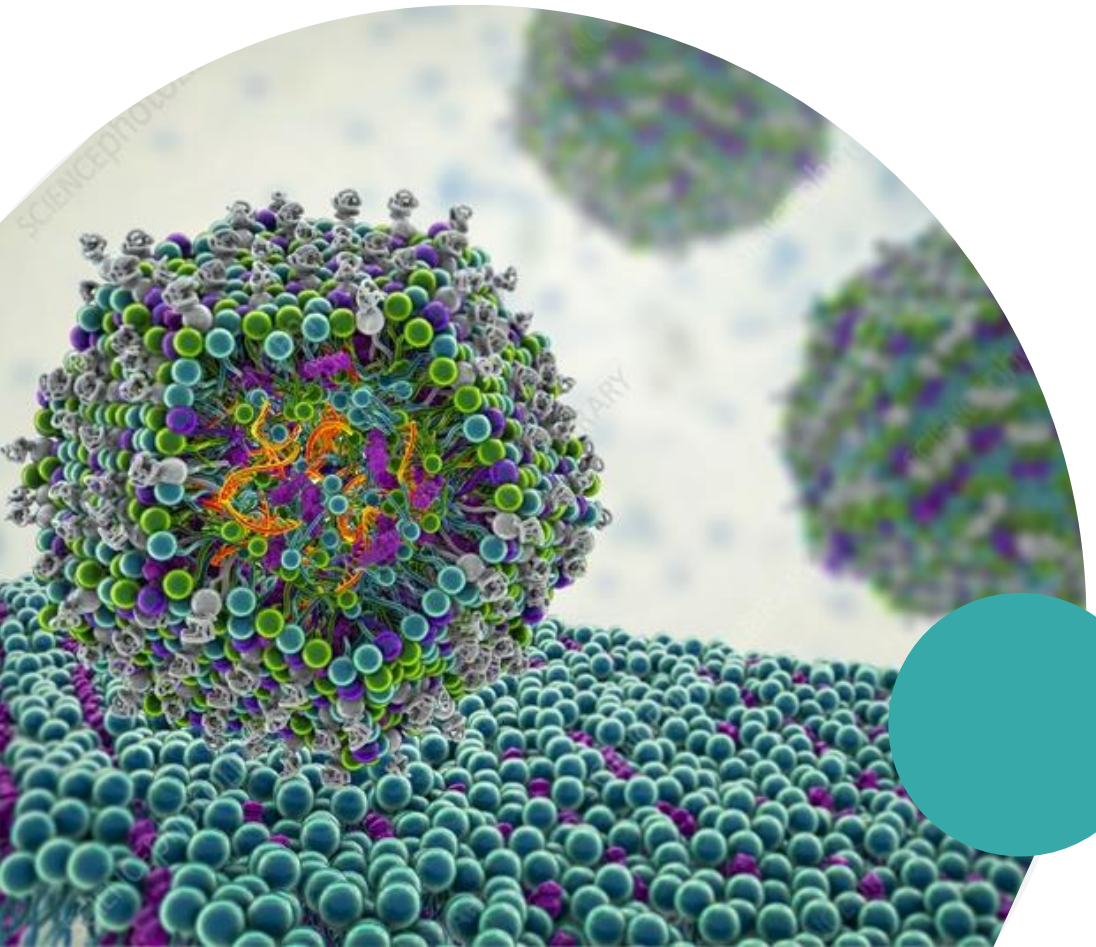
Dengue Vaccine Development



- Partnership with **Prof. Drew Weissman Lab** at University of Pennsylvania
- New R&D lab dedicated for **mRNA by Q1 2024**
- mRNA GMP production facility in design phase
- Capability to produce **raw materials for mRNA** production
  - ✓ T7 RNA polymerase
  - ✓ dNTPs
  - ✓ Cap analog

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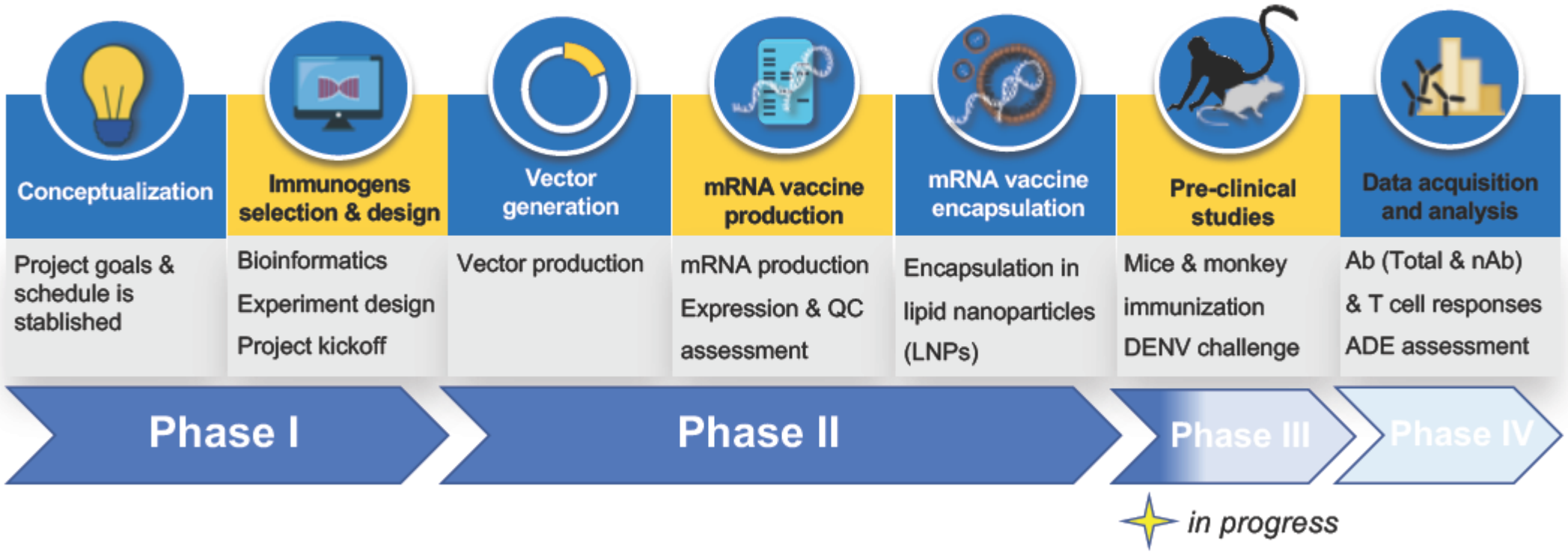
Dengue Vaccine Development

DENV mRNA vaccine development timetable



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Drew Weissman, M.D., Ph.D.
Xiomara Mercado-López, Ph.D.

Dengue Vaccine Development

DENV mRNA vaccine project team

Project leader: Xiomara Mercado-López, Ph.D., MPH

Research technicians:

Wendy Bonilla-Acosta, M.S.

Valeria Bornacelli, M.S.

Perelman School of Medicine
University of Pennsylvania

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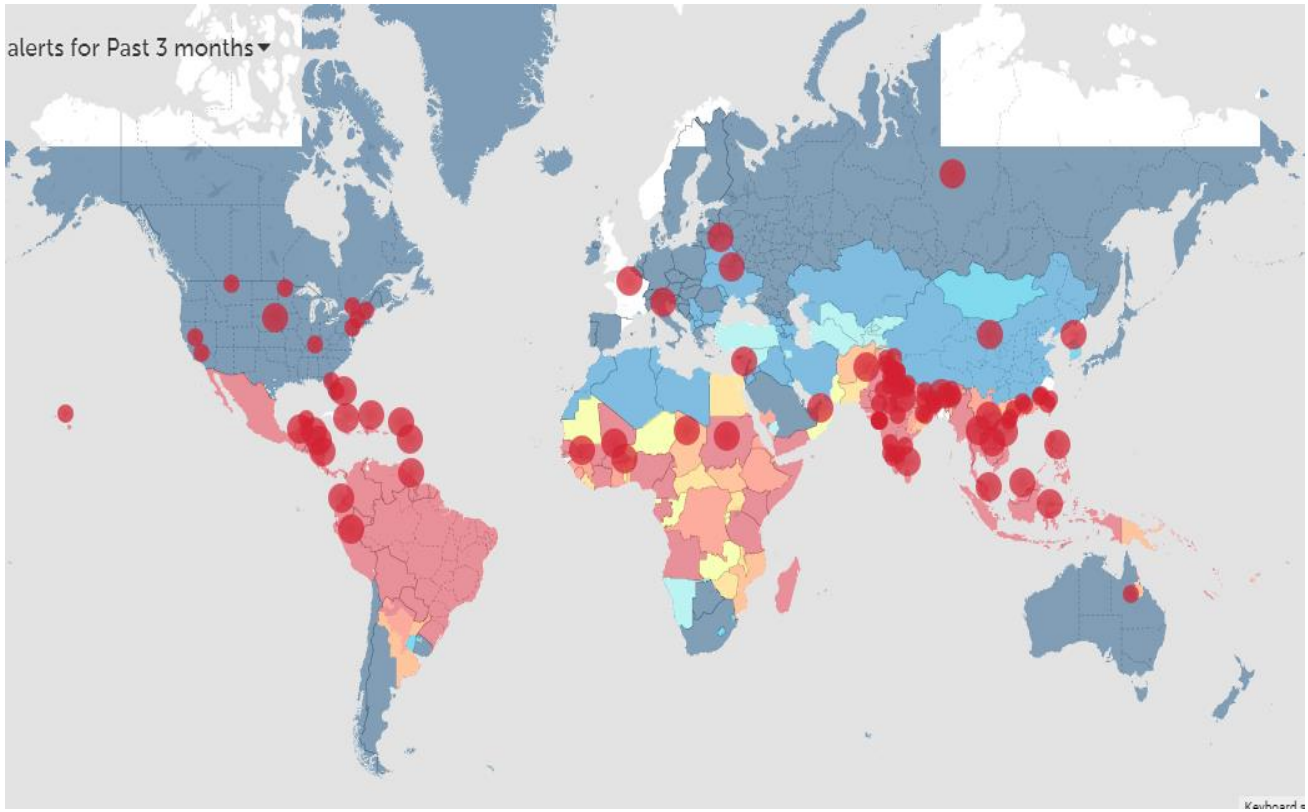
Drew Weissman, M.D., Ph.D.
Xiomara Mercado-López, Ph.D.

Vaccine Research and Trial Opportunities

- Bangladesh had hosted **world largest measles-rubella vaccination campaign**
- **High vaccine acceptance rate** among common people. Ranked among top 15 countries for COVID-19 vaccination
- **Vaccine research and manufacturing facility** at disposal (e.g. Incepta Pharmaceutical Ltd.)
- Globally recognized **CRO for trials** (e.g. icddr'b)



Source: cdc.gov

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- **WHO/MPP/Afrigen**

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